REMARKS

The specification has been amended to replace the existing Sequence Listing with a corrected Sequence Listing. The claims have been amended to address the various informalities noted by the Examiner in the Office Action, as discussed in further detail below. Support for these amendments is as discussed below.

I. Sequence Listing

The Examiner noted that the application contains sequence disclosures that are encompassed by the definitions for amino acid sequences set forth in 37 CFR 1.821 and indicated that the application fails to comply with the requirements of 37 CFR 1.821 to 1.825 regarding sequence disclosures. Specifically, the previously submitted Sequence Listing contains errors as indicated in the attachment to the Office Action.

In response, Applicants have attached paper and computer readable form (CRF) copies of a corrected Sequence Listing in accordance with the Rules. The corrected Sequence Listing includes no new matter. Attached also is the required Statement Under 37 CFR 1.821 (f) confirming that the paper and CRF copies of the Sequence Listing are identical. Applicants believe that they are now in compliance with the requirements of 37 CFR 1.821 to 1.825 regarding sequence disclosures and withdrawal of this objection is respectfully requested.

II. Rejection Under 35 U.S.C. 112, first paragraph

At pages 3 to 5 of the Office Action, Claims 96-99 are rejected under 35 USC 112, first paragraph, as being not enabled by the specification. The Examiner argues that the term "pharmaceutically" and "therapeutically" in the claims implies an assertion of in-vivo therapeutic efficacy allegedly not demonstrated in the application.

Applicants strongly traverse for the reasons already of record. The terms "pharmaceutically acceptable" and "therapeutically acceptable" in the claims is necessary to define the types of salts, esters, carrier media or auxiliary agents that are covered by the claimed invention, and it is a recognized term of art that means "non toxic." In order to advance the prosecution of this case, Applicants have deleted the term "pharmaceutical" and have replaced the terms "pharmaceutically acceptable" and "therapeutically acceptable" in claims 96 and 99 with the equivalent term -- non toxic --, support being found in the application as filed, e.g. page 35, lines 19-21, and inherently found in the original claim language. Since the terms are equivalent, the scope of the claims has not been narrowed by this amendment.

New claim 114 is dependent upon combination claim 99, and recites that the combination further comprises ribavirin, support being found at page 37, lines 21-26, esp. "combinations thereof" at line 26. New claim 115 corresponds to combination claim 99 but recites ribavirin as the additional active agent, support also being found at page 37, lines 21-26, esp. "ribavirin" at line 24.

Method claims 97 and 98 have been deleted and replaced by new method claims 107 to 113, which correspond to the claims 200 to 204 suggested by the Examiner at pages 3 to 4 of the Office Action. Two additional claims have also been added - one corresponding to the Examiner's claim 202 but directed to a mammal (new claim 109) and one corresponding to the Examiner's claim 204 but directed to a human (new claim 113). Support for these claims is found throughout the application as filed, e.g., see pages 35 to 38 regarding methods of use, and the data found in the Tables at pages 113 to 147. Although claims 97 and 98 have been deleted, Applicants believe that the new method claims 113 to 119 fully cover the deleted subject matter. Accordingly, the scope of the method claims has not been narrowed by this amendment.

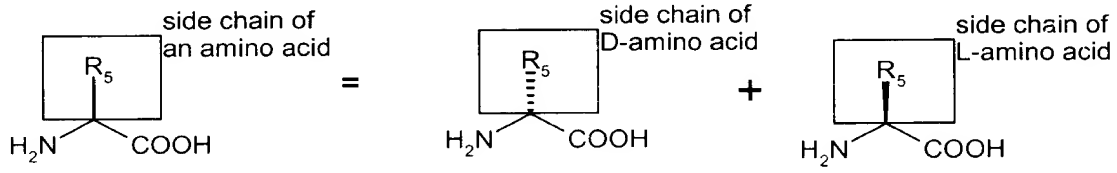
In view of the above, withdrawal of this rejection under 35 USC 112, first paragraph, is respectfully requested.

III. Rejection Under 35 U.S.C. 112, second paragraph

At pages 6 to 8 of the Office Action, various claims are rejected under 35 USC 112, second paragraph, as being indefinite for the reasons outlined below:

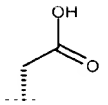
(1) Each of claims 9-11 make reference to the side chains of certain D- or L- amino acids. The Examiner argues that such side chains are indistinguishable, e.g., the side chain of D-aspartic acid is indistinguishable from the side chain of L-aspartic acid, therefore the stereochemistry becomes entirely superfluous. Applicants respectfully disagree.

The reference made to the stereochemistry in claims 9-11 clearly indicates the absolute configuration in which the side chain is oriented.

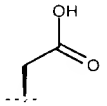


For example, the side chain R_5 can be oriented either down from the plane of the paper (D-amino acid) or up from the plane (L-amino acid). The reference to the absolute configuration of the resulting amino acid clearly indicate in which of these orientations the side chain resides in relation to the peptidic backbone.

To follow the Examiner's example, the side chain of D-Asp as referred to in claim 9 refers to



the following group: ,



whereas the side chain of L-Asp refers to .

Each of them could also have been expressed in terms of their chemical nomenclature such as (*R*) 2-ethanoic acid and (*S*) 2-ethanoic acid respectively. It is well understood by a person skilled in the art that the (*R*)-side chain is clearly distinguished from (*S*)-side chain. Applicants submit that the Examiner's contention that the stereochemistry is superfluous is therefore untenable.

In view of the above, Applicants submit that one skilled in the art would clearly understand what is meant by the D- and L- designations in claims 9-11.

(2) In claim 26, the hyphen at the end of page 153. This has been corrected in amended claim 26.

(3) In claim 30, there should be an "and" before the last Markush member. This has been corrected in claim 30.

(4) In claim 45, the terms "racemic mixture of diastereoisomers" and "racemic mixture of optical isomers" allegedly render the claim indefinite. In response, Claim 45 has been amended to refer to the singular as suggested by the Examiner in order to cover both single compounds as well compounds that are present in mixtures. (Similar amendments have been made in claims 1, 40 and 67). However, the terms "racemic mixture of diastereoisomers" and "racemic mixture of optical isomers" have been retained since they are not considered to be indefinite. Such terms were inserted into claim 45 to provide specific antecedent basis for the language in claim 59, thereby overcoming a previous rejection of claim 59 by the Examiner. The term "racemic mixture" (or "racemate") is well known in organic chemistry and means a mixture of equal quantities of the dextrorotatory (*d-*) and levorotatory (*l-*) isomers of the same compound, and therefore optically inactive. See the relevant definitions found in, e.g., A

Dictionary of Chemistry, 3rd ed. (1996), Oxford University Press; and McGraw-Hill Dictionary of Scientific and Technical Terms, 5th ed. (1994), McGraw-Hill, Inc, copies of which are attached. Accordingly, the terms "racemic mixture of diastereoisomers" and "racemic mixture of optical isomers" would be understood by one skilled in the art to mean, respectively, an optically inactive mixture of diastereoisomers of the same compound or an optically inactive mixture of optical isomers of the same compound. Since these terms would be clearly understood by one of ordinary skill in the art, Applicants submit that claim 45 is not indefinite.

(5) Claim 75 is allegedly indefinite for failing to define the abbreviation "Acca". Applicants disagree and point out that this abbreviation, along with other abbreviations used in the claims, is defined in the specification at page 113, line 18 ("Acca: 1-amino-cyclopropylcarboxylic acid"). Definiteness of claim language is not analyzed in a vacuum but must be analyzed in light of the content of the application disclosure. See MPEP 2173.02. As specifically stated in MPEP 2173.05(a): "The meaning of every term used in a claim should be apparent from the prior art or from the specification and drawings at the time the application was filed. . . .When the specification states the meaning that a term is intended to have, the claim is examined using that meaning . . .". Accordingly, Applicants see no need to amend the claims to include definitions of the abbreviated terms when such abbreviated terms are clearly defined in the specification. The claims must be examined in light of the specification.

(6) In Claim 78, the period should be eliminated as noted. This has been corrected.

(7) In Claim 86, there should be an "and" before the last Markush member. This has been corrected.

(8) Claim 89 is allegedly indefinite for the various reasons as indicated by the Examiner in the Office Action. In response, process claims 89-92 have been canceled and replaced with new claims 103-106, support for the new claims being found in the application as filed, e.g., pages 38-44, Examples 18-36 at pages 78-104, and original claims 89-92. Applicants submit that all the issues raised by the Examiner have been resolved in the new process claims.

(9) Claim 98 was rejected for the abbreviation "NS3". This rejection is moot since claim 98 has been canceled and replaced by the new method claims as suggested by the Examiner.

In view of the above, withdrawal of the rejections under 35 USC 112, second paragraph, is respectfully requested.

IV. Conclusion

In view of the above amendments and remarks, Applicants respectfully submit that this application is now in condition for allowance and earnestly request such action.

If any points remain at issue which can best be resolved by way of a telephonic or personal interview, the Examiner is kindly requested to contact the undersigned attorney at the telephone number listed below.

Respectfully submitted,

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Reg. No. 41,482

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Date: November 14, 2001

Certificate of Mailing
I hereby certify that this correspondence is being deposited with the U.S. Postal Service with sufficient postage as first class mail in an envelope addressed to:
Assistant Commissioner For Patents
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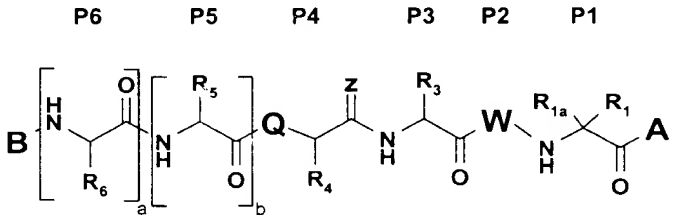
on November 14, 2001.

Philip I. Datlow

AMENDED CLAIMS SHOWING THE CHANGES MADE

1. (Four Times Amended) A compound of formula I or ~~the~~ a racemates, a diastereoisomers or an optical isomers thereof:



(I)

wherein Q is CH_2 or N-Y wherein Y is H or C_{1-6} alkyl;

a) when Q is CH_2, a is 0, b is 0, and B is an amide derivative of formula $R_{11a}N(R_{11b})$-C(O)- wherein R_{11a} is H; C_{1-10} alkyl; C_6 aryl; C_{7-10} alkylaryl; C_{3-7} cycloalkyl or C_{4-8} (alkylcycloalkyl) optionally substituted with carboxyl; or heterocycle-C_{1-6} alkyl;

and R_{11b} is C_{1-6} alkyl substituted with carboxyl, (C_{1-6} alkoxy)carbonyl or phenylmethoxycarbonyl; or C_{7-16} aralkyl substituted on the aromatic portion with carboxyl, (C_{1-6} alkoxy)carbonyl or phenylmethoxycarbonyl;

or R_{11a} and R_{11b} are joined to form a 3 to 7-membered nitrogen-containing ring optionally substituted with carboxyl or (C_{1-6} alkoxy) carbonyl;

or

b) when Q is N-Y, a is 0 or 1, b is 0 or 1, and

B is an acyl derivative of formula R_{11}-C(O)- or a sulfonyl of formula R_{11}-SO_2 wherein

R_{11} is (i) C_{1-10} alkyl optionally substituted with carboxyl or C_{1-6} alkanoyloxy; C_{1-6} alkoxy; or carboxyl substituted with 1 to 3 C_{1-6} alkyl substituents;

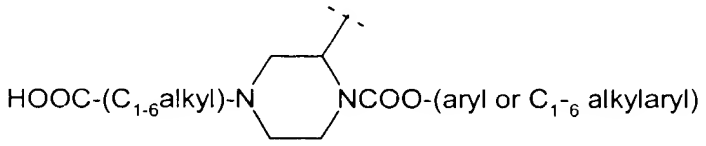
(ii) C_{3-7} cycloalkyl or C_{4-10} alkylcycloalkyl, both optionally substituted with carboxyl,

(C_{1-6} alkoxy)carbonyl or phenylmethoxycarbonyl;

(iii) C_6 or C_{10} aryl or C_{7-16} aralkyl optionally substituted with C_{1-6} alkyl, hydroxy, or amino optionally substituted with C_{1-6} alkyl; or

(iv) Het optionally substituted with C_{1-6} alkyl, hydroxy, amino optionally

substituted with C_{1-6} alkyl, or amido optionally substituted with C_{1-6} alkyl,



or ,

R_6, when present, is C_{1-6} alkyl substituted with carboxyl;

R_5, when present, is C_{1-6} alkyl optionally substituted with carboxyl;

and

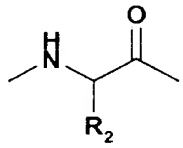
c) when Q is either CH_2 or N-Y, then

R_4 is C_{1-10} alkyl, C_{3-7} cycloalkyl or C_{4-10} (alkylcycloalkyl);

z is oxo or thioxo;

R_3 is C_{1-10} alkyl optionally substituted with carboxyl, C_{3-7} cycloalkyl or C_{4-10} (alkylcycloalkyl);

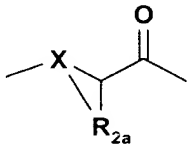
W is a group of formula II:



Formula II

wherein R_2 is C_{1-10} alkyl or C_{3-10} cycloalkyl optionally substituted with carboxyl or an ester or amide thereof; C_6 or C_{10} aryl or C_{7-16} aralkyl; or

W is a group of formula IIa:



Formula IIa

wherein X is CH or N; and

R_{2a} is divalent C_{3-4} alkylene which together with X and the carbon atom to which X and R_{2a} are attached form a 5- or 6-membered ring, said ring optionally substituted with OH; SH; NH_2; carboxyl; R_{12}; CH_2-R_{12}, OR_{12}, $C(O)OR_{12}$, SR_{12}, NHR_{12} or $NR_{12}R_{12a}$;

wherein R_{12} and R_{12a} are independently a saturated or unsaturated C_{3-7} cycloalkyl or C_{4-10} (alkyl cycloalkyl) being optionally mono-, di- or tri-substituted with R_{15}, or R_{12} and R_{12a} is a C_6 or C_{10} aryl or C_{7-16} aralkyl optionally mono-, di- or tri-

substituted with R_{15}, or R_{12} and R_{12a} is Het or (lower alkyl)-Het optionally mono-, di- or tri-substituted with R_{15},

wherein each R_{15} is independently C_{1-6} alkyl; C_{1-6} alkoxy; amino optionally mono- or di-substituted with C_{1-6} alkyl; sulfonyl; NO_2; OH; SH; halo; haloalkyl; amido optionally mono-substituted with C_{1-6} alkyl, C_6 or C_{10} aryl, C_{7-16} aralkyl, Het or (lower alkyl)-Het; carboxyl; carboxy(lower alkyl); C_6 or C_{10} aryl, C_{7-16} aralkyl or Het, said aryl, aralkyl or Het being optionally substituted with R_{16};

wherein R_{16} is C_{1-6} alkyl; C_{1-6} alkoxy; amino optionally mono- or di-substituted with C_{1-6} alkyl; sulfonyl; NO_2; CH; SH; halo; haloalkyl; carboxyl; amide; or (lower alkyl)amide;

or X is CH or N; and R_{2a} is a divalent C_{3-4} alkylene which together with X and the carbon atom to which X and R_{2a} are attached form a 5- or 6-membered ring which in turn is fused with a second 5-, 6- or 7-membered ring to form a bicyclic system wherein the second ring is substituted with OR_{12a}, wherein R_{12a} is C_{7-16} aralkyl;

R_{1a} is hydrogen, and R_1 is the side chain of an amino acid selected from the group consisting of cysteine (Cys), aminobutyric acid (Abu), norvaline (Nva) and allylglycine (AlGly); or

R_{1a} and R_1 together form a 3- to 6-membered ring optionally substituted with R_{14} wherein R_{14} is C_{1-6} alkyl, C_{3-5} cycloalkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_6 aryl or C_{7-10} aralkyl all optionally substituted with halo; and

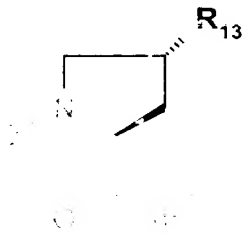
A is hydroxy; or C_{1-6} alkylamino, di(C_{1-6} alkyl)amino or phenyl-C_{1-6} alkylamino;

wherein Het is a five-, six-, or seven-membered saturated or unsaturated, including aromatic, heterocycle containing from one to four heteroatoms selected from nitrogen, oxygen and sulfur, which heterocycle is optionally fused to a benzene ring;

or a non-toxic salt or ester thereof.

26. (Amended) The compound of formula I according to claim 25, wherein R_{2a} is the side chain of proline substituted with R_{13} at the 4-position with the stereochemistry shown in

formula IIIa:



(IIIa)

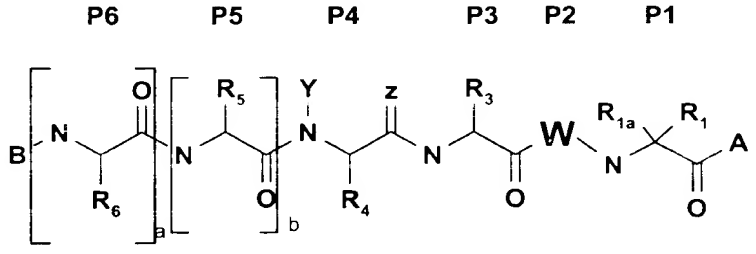
wherein R_{13} is S-R_{12} or O-R_{12} wherein R_{12} is a C_6 or C_{10} aryl, C_{7-16} aralkyl, Het or -CH_2-Het, all optionally mono-, di- or tri-substituted with R_{15},

wherein R_{15} is C_{1-6} alkyl; C_{1-6} alkoxy; amino; di(lower alkyl)amino; (lower alkyl)amide; C_6 or C_{10} aryl, or Het, said aryl or Het being optionally substituted with R_{16}, and

R_{16} is C_{1-6} alkoxy; amino; di(lower alkyl)amino; (lower alkyl)amide; halo; or trifluoromethyl.

30. (Twice Amended) The compound of formula I according to claim 1, wherein R_{1a} is hydrogen and R_1 is the side chain of the amino acid selected from the group consisting of: cysteine (Cys), aminobutyric acid (Abu), norvaline (Nva), ~~or~~ and allylglycine (AlGly).

40. (Twice Amended) A compound of formula (IA) or ~~the~~ a racemates, a diastereoisomers or an optical isomers thereof:



(IA)

wherein Y is H or C_{1-6} alkyl;

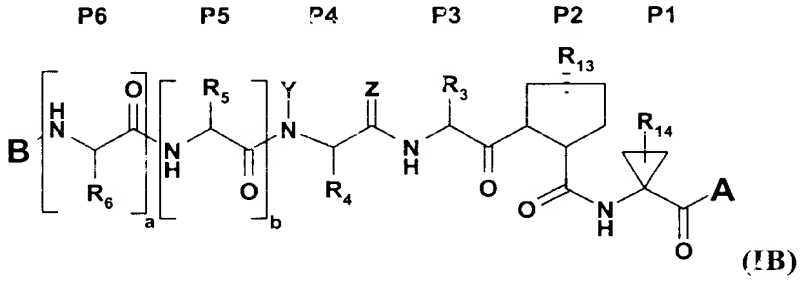
a is 0 or 1;

b is 0 or 1;

B is as defined in claim 1, paragraph b);

R_6, R_5, R_4, z, R_3, W, R_1, R_{1a} and A are as defined in claim 1.

45. (Three Times Amended) A compound of formula IE or ~~the~~ a diastereoisomers, an optical isomers, a racemic mixture of diastereoisomers or a racemic mixture of optical isomers thereof:



(IB)

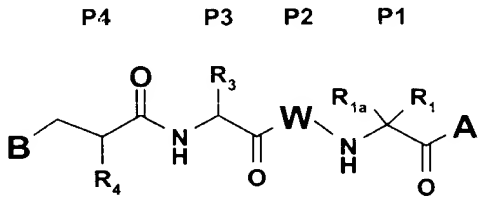
wherein

B, a, b, R_6, R_5, Y, R_4, Z, R_3, and A are as defined in claim 1,

R_{13} is R_{12}, OR_{12}, $C(O)OR_{12}$, SR_{12}, NHR_{12} or $NR_{12}R_{12a}$ wherein R_{12} and R_{12a} are as defined in claim 1; and

R_{14} is C_{1-6} alkyl, C_{2-6} alkenyl optionally substituted with halogen; C_{6-10} aryl or C_{7-10} aralkyl optionally substituted with halogen; or a non-toxic salt or ester thereof.

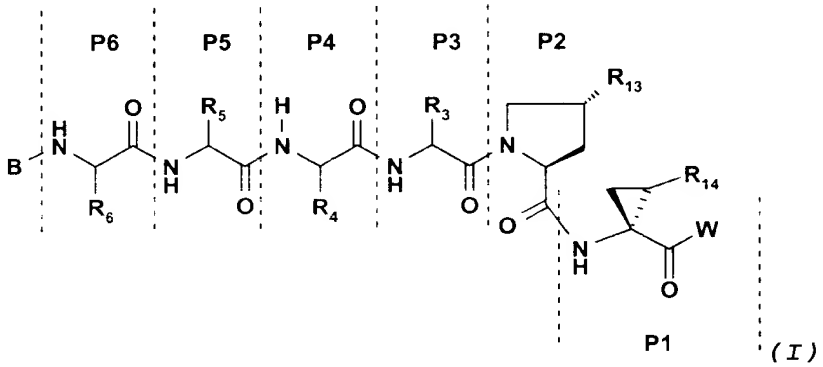
67. (Twice Amended) A compound of formula IC or ~~the~~ a racemates, a diastereoisomers or an optical isomers thereof:



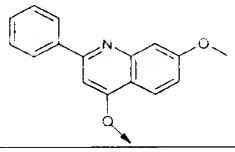
wherein B is as defined in claim 1, paragraph a);

R_4, R_3, W, R_{1a}, R_1, and A are as defined in claim 1.

78. (Amended) A compound of formula (I):



wherein B, P6, P5, P4, P3, R_{13}, and R_{14} are as defined below, said compound selected from the group consisting of:

Tab. 7 Cpd#	B	P6	P5	P4	P3	R_{13}	R_{14}	W
701	Ac	Asp	D-Glu	Ile	Val	OBn	Et	NH-(*S*)-CHMePh
and 702	Dnl	Asp	D-Glu	Chg	Tbg		vinyl	OH

86. (Amended) A tetrapeptide of formula I according to claim 77, selected from the group consisting of compound #: 602; 603; 605; 606; 607; 608; 609; 610; 611; 614; 615; 616; 618; 619; 620; 621; 623; 624; 625; 626; 628; 629; 630; 631; 632; 633; 634; and

635.

96. (Twice Amended) A ~~pharmaceutical~~ composition comprising an anti-hepatitis C virally effective amount of a compound of formula I according to claim 1, or a ~~pharmaceutically acceptable~~non-toxic salt or ester thereof, in admixture with a ~~pharmaceutically acceptable~~non-toxic carrier medium or auxiliary agent.

99. (Amended) A ~~pharmaceutical~~ combination comprising a compound of formula I according to claim 1, or a ~~therapeutically acceptable~~non-toxic salt or ester thereof, and an interferon in admixture with a ~~pharmaceutically acceptable~~non-toxic carrier medium or auxiliary agent.